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Y ROCKY TSAO
FISH & RICHARDSON PC
225 FRANKLIN STREET
BOSTON, MA 021102804

EXAMINER
DEVI, SARVAMANGALA J N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/412,558	Applicant(s) Hwang et al.
	Examiner S. Devi, Ph.D.	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 21, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-23* is/~~are~~ pending in the application.

4a) Of the above, claim(s) *1-13, 16, and 19-23* is/~~are~~ withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *14, 15, 17, and 18* is/~~are~~ rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments filed 09/25/01 (paper no. 7) and 02/21/02 (paper no. 9). With this, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' election filed 09/25/01 (paper no. 7) in response to the restriction requirement mailed 09/25/01 (paper no. 6). Applicants elect invention III, claim 15, without traverse.

Status of Claims

3) Claims 1-23 are pending in this application.

Claims 14, 15, 17 and 18 have been amended via the amendment filed 09/25/01.

Claims 1-13, 16 and 19-23 have been withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claim 15 has been elected. The linking claims 14, 17 and 18 have been joined with the elected claim 15.

Claims 14, 15, 17 and 18 are under examination. An Action on the Merits for these claims is issued in the instant Office Action (paper no. 10).

Sequence Listing

4) Acknowledgment is made of Applicants' Sequence Listing, which has been entered.

Information Disclosure Statement

5) Acknowledgment is made of Applicants' Information Disclosure Statement filed 02/10/99 (paper no. 2). The information referred to therein has been considered and a signed copy of the same is attached to this Office Action (paper no. 10).

Drawings

6) The drawings are objected to because of the problems noted by the Draftsperson in the attached Form PTO 948 (paper no. 10). Correction is required.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

7) Claims 14, 15, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 14, 15, 17 and 18 are vague in the recitation "*Pseudomonas* exotoxin A", because the claims fail to particularly point out and distinctly claim the subject of the invention. It is unclear the exotoxin A of which species of *Pseudomonas* the limitation represents.

(b) Claims 14, 15, 17 and 18 are further vague and confusing in the recitation "**a** receptor binding domain of **a** *Pseudomonas* exotoxin A" [Emphasis added], because the recitation "a" conveys that there are more than one receptor binding domains and more than one exotoxin A. For clarity and in order to distinctly claim the subject matter of the invention, it is suggested that Applicants replace the recitation with --the receptor binding domain of *Pseudomonas aeruginosa* exotoxin A--.

Rejection(s) under 35 U.S.C. § 102

8) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> **(e)** The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9) Claims 14 and 18 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lorberboum-Galski *et al.* (US 6,140,066, filed 24 March 1998).

Lorberboum-Galski *et al.* disclose a DNA sequence encoding a polypeptide comprising a full length *Pseudomonas* exotoxin A (PE) and two copies of a peptide sequence, gly-gly-gly-gly-ser, in a consecutive series (see Figure 1; 'Brief Description' for Figure 1; first full paragraph under 'EXAMPLE'; and column 10, lines 42-45). That the prior art full length *Pseudomonas* exotoxin A 'comprises' a receptor binding domain of *Pseudomonas* exotoxin A is inherent from the teachings of Lorberboum-Galski *et al.*

Claims 14 and 18 are anticipated by Lorberboum-Galski *et al.*

10) Claims 14, 15 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hickey *et al.* (WO 97/15325).

Hickey *et al.* teach GnRH-PE chimeric hybrid proteins produced by recombinant DNA technology (see third full paragraph on page 6; second full paragraph on page 7; page 12, third full paragraph; and last paragraph on page 10). The GnRH peptide has the amino acid sequence of SEQ ID NO: 1 (see second full paragraph on page 8). The hybrid proteins contain contiguous sequences of the constituent proteins/peptides (see page 29, second full paragraph). The hybrid GnRH protein manufactured by recombinant DNA techniques preferably comprises two native GnRH molecules in tandem (see page 9, lines 29-32). The recombinant DNA encoding the hybrid proteins of the invention are taught on page 20, 21, 29 and 30.

Claims 14, 15 and 18 are anticipated by Hickey *et al.*

11) Claims 14, 17 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hwang *et al.* (*Cell* 48: 129-136, 1987 - Applicants' IDS) (Hwang *et al.*, 1987) or Hwang *et al.* (*J. Biol. Chem.* 264: 2379-2384, 1989 - Applicants' IDS) (Hwang *et al.*, 1989).

It is noted that the instant claims encompass both an isolated and/or purified as well as a non-isolated and/or non-purified nucleic acid. Therefore, a plasmid, a vector or a host cell comprising the nucleic acid reads on the claimed nucleic acid. It is further noted that the instant claims do not specifically recite the length of the 'peptide sequence' and therefore, even a single amino acid residue constitutes a peptide sequence. The 'peptide sequence', as recited currently, encompasses an antigenic or immunogenic as well as a non-antigenic or non-immunogenic peptide sequence. It is also noted that the instant specification describes that the domain Ia of PE comprises amino acid residues 1-252 (see page 2, first paragraph of the specification).

Hwang *et al.* (1987) teach a recombinant molecule comprising a nucleic acid sequence, pJH13, encoding a polypeptide comprising full domain I, half of domain II and entire domain III of PE (see right column on page 130). It is taught that the functional domain Ia contains amino acid residues 1 to 252 and is the cell recognition domain (see abstract; and right column on page 129). Thus, Hwang's (1987) nucleic acid molecule inherently comprises the receptor binding

domain of *Pseudomonas* exotoxin A as well as half of domain II and entire domain III of PE.

Hwang *et al.* (1989) teach an expression plasmid molecule pJH4 which encodes a PE molecule, which comprises domain Ia, the cell binding domain, as well as domain II and domain III (see page 2379). Hwang *et al.* (1989) teach a BL21 (DE3) containing pJH4 expression plasmid which expresses a PE molecule (see right column on page 2379).

Since the instant claims do not specifically recite the length of the 'peptide sequence', even a singe amino acid residue constitutes a peptide sequence. Therefore, Hwang's (1987 or 1989) domain II and domain III inherently contain at least two or ten discontinuous copies of a single amino acid residue, or at least two consecutive single amino acid-long peptide sequences, and thus meet the structural element (2) of the instant claims.

Claims 14, 17 and 18 are anticipated by Hwang *et al.* (1987) or Hwang *et al.* (1989).

Rejection(s) under 35 U.S.C. § 103

12) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

13) Claims 14, 15, 17 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Potter *et al.* (WO 96/24675, published 15 August 1996) or Russell-Jones *et al.* (WO 91/02799) in view of Hwang *et al.* (*J. Biol. Chem.* 264: 2379-2384, 1989 - Applicants' IDS) (Hwang *et al.*, 1989) and Pastan *et al.* (US 4,892,827).

Potter *et al.* teach the concept of genetically fusing multiple copies of GnRH with a bacterial toxin or a portion thereof and the use of expressed recombinant chimeric or fusion protein as an effective vaccine. Potter *et al.* teach a nucleic acid encoding a polypeptide which comprises copies, repeats or multimers of non-consecutive, or consecutive or repetitive, GnRH and a bacterial leukotoxin (see abstract; and pages 19 and 22). Potter *et al.* disclose that the presentation of the peptide antigen in multiple copies generally enhances immunogenicity (see last paragraph on page 3). A selected leukotoxin polypeptide sequence imparts enhanced immunogenicity to a fused GnRH multimer by providing T-cell epitopes. The leukotoxin polypeptide lacking leukotoxic activity yet retaining immunogenicity and at least one T cell epitope is desirable (see page 13 and 14). The GnRH multimeric DNA constructs consist of [GnRH]n wherein n is greater than 1 copy (i.e., inclusive to 10 to 20 copies), for instance, 2, 4 or 8 copies (see pages 6 and 7; last paragraph on page 11; and Figure 1). The toxin used in the fusion can be a truncated toxin (see page 8, third full paragraph).

Russell-Jones *et al.* disclose recombinant DNA fusion constructs comprising tandem repeats of LHRH (i.e., GnRH) analogues to a sequences of TraTp or TraTp analogues which serve as a self-adjuvanting carrier (see page 3 and 6; page 4, lines 21 and 22; Example 1). Preferably the LHRH analogue peptide in the fusion comprises at least one (i.e., inclusive of 10 or 20) of the following sequence: Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly (i.e, SEQ ID NO: 1) (see pages 7 and 10-13). LHRH sequences used in the fusion can be dimers (see Figure 4 and page 13) or multimers (see Figure 5; Table 1; and pages 13 and 21). See Examples 1 and 6; and claims 5-9 and 12-14. Russell-Jones *et al.* expressly teach that insertion of tandem repeats of LHRH analogues (i.e., peptide sequences) gives more immunogenic fusion than the insertion of a single insert (see page 6, lines 26-29).

Potter *et al.* or Russell-Jones *et al.* do not teach a nucleic acid encoding a polypeptide comprising the peptide of SEQ ID NO: 1 and a receptor binding domain of a *Pseudomonas* exotoxin A.

Hwang *et al.* (1989) teach a nucleic acid sequence encoding domain Ia of PE. Hwang *et al.* teach that domain Ia of PE can be used for vaccination against PE-mediated cytotoxicity (see

right column on page 2379).

Pastan *et al.* teach recombinant gene fusions using PE (see column 6, lines 30 and 31). Pastan *et al.* teach pJH14 plasmid that encodes structural domain Ia of PE comprising amino acids 1-252 (see column 6, lines 60 and 61). Pastan *et al.* teach that domain Ia of PE exhibits greatly diminished toxicity in mice (see column 6, lines 21, 22, 27 and 28). Pastan *et al.* expressly teach the fusion of PE or part of PE with other polypeptides, including luteinizing hormone (see column 6, lines 36-43). Pastan *et al.* specifically teach that the protein encoded by domain I could be administered to patients to treat pseudomonas sepsis, because it would block toxin binding to cells (see column 1, lines 15-18).

Given the Hwang's (1989) express teaching that domain Ia of PE can be used for vaccination, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace the leukotoxin or truncated leukotoxin sequence in Potter's multimeric GnRH-leukotoxin fusion nucleic acid construct , or the TraTp sequence in Russell-Jones' LHRH-TraTp DNA fusion construct with Pastan's or Hwang's nucleic acid sequence encoding domain Ia of PE, to produce the nucleic acid of the instant invention, with a reasonable expectation of success, because Pastan *et al.* expressly teach that PE fusion can be performed with a luteinizing hormone. One skilled in the art would understand that Potter's or Russell-Jones' GnRH or LHRH qualifies as a luteinizing hormone. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of producing a fusion nucleic acid construct that encodes a GnRH fusion polypeptide which exhibits greatly diminished toxicity and which is also therapeutic against *Pseudomonas* as taught by Pastan *et al.* Substitution of a nucleic acid encoding one bacterial toxin sequence or one bacterial protein sequence with another, alternative, art-known bacterial toxin or bacterial protein sequence would have been obvious to one of ordinary skill in the art and would have brought about similar results or effects.

Claims 14, 15, 17 and 18 are *prima facie* obvious over the prior art of record.

Pertinent Prior Art

14) The prior art made of record and not relied upon currently in any of the rejections are

considered pertinent to Applicants' disclosure.

- Meloen *et al.* (*Vaccine* 12: 741-746,1994) teach an immunogen wherein tandem repeats of the amino acid sequence of the GnRH peptide were fused or conjugated to a protein carrier, such as KLH, for vaccination purposes (see abstract; and Materials and Methods'). Meloen *et al.* teach that GnRH is a self molecule which is normally not 'seen' by the immune system. Consequently, it is insufficiently immunogenic, i.e., unable to induce sufficient antibody response against endogenous GnRH. Meloen *et al.* identified the real need for a more immunogenic GnRH-like antigen (see page 741).

- Chen *et al.* (*Appl. Microbiol. Biotechnol.* 52: 524-533, October 1999) teach a gene fragment contained in the plasmid, pET15bJIF, which expresses a protein or polypeptide comprising $(His)_6$-PE(1-405)-OprI(19-83)-LE-Opr(24-350) or PEIF. Chen *et al.* teach the pET-15bJMx which encodes the full length PE with a $(His)_6$ tag (see page 525, right column and Figure 2). Figure 2 shows that PEIF comprises Ia domain, i.e., the receptor binding domain of PE.

Remarks

15) Claims 14, 15, 17 and 18 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

May, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER